Attenuation of Pain in a Randomized Trial by Suppression of Peripheral Nociceptive Activity in the Immediate Postoperative Period

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Abstract

Peripheral neuronal barrage from tissue injury produces central nervous system changes contributing to the maintenance of postoperative pain. The therapeutic approaches to blocking these central changes remain controversial as previous studies have not differentiated presurgical interventions from those administered after tissue injury, yet prior to pain onset. The present study evaluated the relative contributions of blockade of nociceptive input intraoperatively or during the immediate postoperative period on pain suppression. Subjects were randomly allocated to one of four groups: preoperative 2% lidocaine, postoperative 0.5% bupivacaine, both, or placebo injections. General anesthesia was induced and third molars extracted. Pain was assessed over 4 hr, at 24 and 48 hr. Blood samples collected for measurement of ß-endorphin increased two-fold during surgery, indicative of activation of the peripheral nociceptive barrage in response to painful stimuli. Pain was lower in the immediate postoperative period in the bupivacaine groups while increasing in the lidocaine group over time. Pain intensity was lower 48 hr after surgery in the groups whose postoperative pain was blocked by administration of bupivacaine, but no effect was demonstrated for preoperative administration of lidocaine alone. These results in the oral surgery pain model suggest that minimizing the peripheral nociceptive barrage during the immediate postoperative period decreases pain at later time periods. In contrast, blocking the intraoperative nociceptive barrage does not appear to contribute significantly to the subsequent reduction in pain.

Key words: sensitization, , central plasticity, preemptive analgesia, oral surgery model

Implication Statement**:** Suppression of postoperative pain immediately following surgery attenuates the pain experienced one to two days after surgery. These findings suggest that pain following minor

surgery can be prevented by blocking development of pain processes which amplify pain for days after surgery.

Introduction

Tissue injury produces a barrage of nociceptive input to the nervous system, producing sensory changes characterized by prolonged pain, an increased sensitivity to painful stimuli (hyperalgesia), and pain following innocuous stimuli (allodynia)(1). These changes persist long after the initial injury and appear to occur within the central nervous system at the level of the spinal cord and possibly elsewhere(1,2). The response properties of spinal dorsal horn neurons are changed following tissue injury to result in enlarged receptive fields and increased excitability (3,4). The increase in excitability involves activation of N-methyl-D-aspartate (NMDA) receptors by excitatory amino acids such as glutamate and aspartate (5,6) and neuropeptides substance P and calcitonin gene-related peptide (7). It has been proposed that release of excitatory amino acids at sites within the central nervous system leads to activation of NMDA receptor sites and excessive depolarization contributing to the expansion of receptive fields and hyperexcitability, thereby leading to an amplification of pain and an increase in its duration (8). These changes in the central nervous system initiated by afferent nociceptive barrage are characterized as central sensitization or central hyperexcitability and contribute to postoperative pain.

Demonstration of central sensitization in animal models following tissue injury and its reduction by administration of opioids or local anesthetics administered prior to tissue injury (2,9,10) led to clinical studies evaluating this phenomenon in humans. Prospective clinical studies demonstrated that preincisional administration of a local anesthetic reduces pain in comparison to surgery performed without local anesthesia (11) or postoperative infiltration of local anesthetic (12). We previously demonstrated that administration of the long-acting local anesthetic bupivacaine in comparison to a saline placebo prior to oral surgery suppresses the intraoperative release of pituitary ß-endorphin, an index of central nociceptive input, and results in reduced spontaneous pain report at 48 hr (13). Pain and plasma ß-endorphin levels were elevated at one hr postoperatively in the placebo group, indicating a continued afferent nociceptive barrage following surgery that may have contributed to the development of central sensitization. However, that study did not differentiate between the pre-emptive effect of the long-acting local anesthetic bupivacaine and its carry-over into the postoperative period. The present study was designed to selectively block intraoperative nociceptive input, postoperative

pain, or both using a before and after factorial design as recommended by Katz (14) and Kissin (15). The results demonstrate that reducing pain in the immediate postoperative period is more effective for minimizing the establishment of central sensitization than is blocking the intraoperative afferent barrage after oral surgery.

Materials and Methods

Subjects were oral surgery outpatients undergoing the surgical removal of 2-4 third molars who had expressed a preference for general anesthesia at the time of their initial screening visit. Inclusion criteria included the presence of two partial or full bony impacted third molars; and missing, erupted or soft-tissue impacted maxillary third molars, in order to maximize pain generated from the mandible and minimize that from the maxilla. Subjects were free of systemic disease, not taking any concomitant analgesic medications, and provided informed consent to the risks of the surgical procedure, general anesthesia, and participation in the study. The clinical protocol and informed consent document were approved by the Institutional Review Board of the National Institute of Dental and Craniofacial Research, National Institutes of Health.

On the day of surgery a blood sample was drawn for baseline measurement of plasma ß-endorphin 20 min after venipuncture. Patients were then premedicated with a sedative dose of midazolam (mean dose = 3.0 $\pm$ 1.3 mg) to alleviate anxiety (Fig. 1). Local anesthetic or saline placebo were randomly allocated and administered prior to and at the end of surgery in a double-blind, parallel groups factorial design to result in four treatment groups: preoperative administration of 2% lidocaine with 1:200,000 epinephrine and postoperative injection of saline with epinephrine 1:200,000 (preoperative local anesthesia group); preoperative saline placebo and postoperative 0.5% bupivacaine, both with 1:200,000 epinephrine (postoperative local anesthesia group); preoperative 2% lidocaine and postoperative 0.5% bupivacaine, both with 1:200,000 epinephrine (pre- and postoperative local anesthesia group); or preoperative and postoperative saline with 1:200,000 epinephrine injections (no local anesthesia group). After 5 min, with the oral surgeon outside the room, an unblinded observer assessed the efficacy of mandibular block for all subjects by probing the retromolar area with a sharp dental instrument and questioning the patient for the presence of the normal signs of local anesthesia (parethesia of the lower lip and absence of pain upon noxious stimulation). If the regional anesthesia was not

complete in subjects administered lidocaine, the anesthetic was readministered and the efficacy assessed again after 5 min.

General anesthesia was then induced with propofol and succinylcholine. A blood sample was obtained following intubation to examine the changes in circulating ß-endorphin due to the anesthetic drugs and the stimulus of intubation. Anesthesia was maintained with propofol and 60% nitrous oxide while the third molars were surgically extracted. Blood samples were obtained immediately following the last tooth extraction to examine the effects of the surgical stimulus on circulating ß-endorphin levels. Local anesthesia or placebo was administered at the end of surgery according to the randomizaton scheme consisting of either 0.5% bupivacaine or saline injections with 1:200,000 epinephrine. Additional blood samples were collected at 1, 2, 3, and 4 hr postoperatively.

Subjects remained at the clinic to permit collection of postoperative blood samples and to ensure compliance with instructions for administration of the initial dose of analgesic. Pain medication (acetaminophen 975 mg) was administered in the postoperative period if requested for the relief of moderate or severe pain. The duration of bupivacaine with epinephrine for mandibular nerve block is 6-8 hr as compared to 2-3 hr duration of nerve block for lidocaine with epinephrine (16). Patients were dispensed acetaminophen with instructions to take three tablets (975 mg) every 6 hr by the clock, and codeine 30 mg to be taken only if needed for unrelieved pain.

Subjects recorded analgesic drug intake in a medication diary and completed pain questionnaires consisting of a 100 mm visual analog scale (VAS), and 200 mm verbal descriptor scales (14) for pain intensity and the affective component of pain over the postoperative observation period, and upon awakening at 24 and 48 hr, prior to ingestion of any analgesics. The 100 mm VAS was anchored by the words “none” and “worst possible pain” and subjects instructed to “rate their pain intensity at this time.” The verbal descriptor scale for pain intensity consists of a 200 mm vertical bar with 12 verbal descriptors ranging from “weak,” “mild,” and “moderate” to “strong,” “intense,” and “very intense” spaced along the scale at intervals based on previous psychophysical rankings of their relative magnitude (17, 18, 19) The verbal

descriptor scale for the affective component of pain substituted similarly spaced verbal descriptors including “unpleasant,” “annoying,” distressing,” and “intolerable.” Subjects were instructed to mark the point on the scales that best corresponded to the intensity and unpleasantness of the pain that they were experiencing. Verbal descriptor scales are sensitive to small differences in nociceptive stimuli (18) and are useful for measuring pain report in sedated outpatients (20), similar to subjects emerging from general anesthesia. Subjects were contacted by phone at 24 hr postoperatively and returned to the clinic at 48 hr postoperatively to submit the pain ratings and medication diaries, and to assess compliance with the medication regimen through a pill count.

Blood samples were collected into chilled tubes containing 0.1 ml 15% EDTA, centrifuged under refrigeration, frozen on dry ice, and stored at -80^{o} C. Plasma samples (200 µl) were analyzed in duplicate by immunoradiometric (i.r.) assay (Nichols Institute Diagnostics B.V., Wijchen, The Netherlands), a method whereby the sample is incubated with antibody and ^{125}I-labeled antibody to form a solid phase antibody - ß-endorphin - labeled antibody complex. After unbound material is removed, the radioactivity is measured with a gamma counter. The concentration of ß-endorphin is directly proportional to the radioactivity measured and is quantified by comparing the samples to the standard curve obtained in the same assay with known human ß-endorphin standards. The limit of detection for the assay was 12.5 pg/ml.

A total of N=110 subjects were enrolled ; six were not randomized after enrollment as they did not return to the clinic for surgery. Of the 104 subjects randomized to a treatment group, five reported paresthesia of the inferior alveolar nerve subsequent to surgery, consistent with surgical trauma. An additional nine subjects who were administered bupivacaine at the conclusion of surgery while still under general anesthesia did not display signs of mandibular anesthesia at any

of the postoperative observations. These data were not analyzed due to the ineffective intervention. The remaining 90 subjects did not differ for the mean demographic, surgical and anesthetic variables across the four groups (Tables 1 and 2).

Data were analyzed with the BMDP Statistical Software Package (SPSS Inc., Chicago IL). Statistical differences between the four groups were determined by two-way analysis of variance for the results of the VAS and the verbal descriptor scales. Surgical variables, the doses of anesthetic drugs, demographic variables (age, height, weight) and ß-endorphin levels were analyzed among groups by one-way analysis of variance and Duncan's multiple range test. For all statistical tests, differences were accepted as significant if the probability of occurrence by chance alone was less than 5% ($P < 0.05$) in a two-tailed test.

Results

Plasma ß-endorphin concentrations increased significantly during surgery in the subjects receiving the saline injections preoperatively (Fig. 2), indicative of a nociceptive barrage sufficient to activate pituitary ß-endorphin release. Plasma ß-endorphin remained significantly elevated at 60 min post-surgery in the placebo group consistent with postoperative pain that was blocked in the other three groups by local anesthesia. ß-endorphin decreased in the group receiving bupivacaine at the end of surgery in the sample collected at 1 hr post-surgery, consistent with blockade of postoperative pain as subjects recovered from the effects of the general anesthesia. ß-endorphin did not increase during surgery in the two groups receiving lidocaine preoperatively (Fig. 2). Levels remained significantly lower at the 60 min postoperative sample in the three groups receiving local anesthetic in comparison to the placebo group. The plasma concentrations of ß-endorphin increased in individual patients at varying times over the remaining three hours of the observation period as the local anesthetic effects

dissipated and subjects reported postoperative pain. Administration of rescue analgesic subsequently decreased pain report and plasma ß-endorphin in individual subjects, confounding any mean differences among the groups at the 2 to 4 hr time points (Table 4).

Acute pain over the first four hours post-surgery (Fig. 3, upper panel) was significantly lower in the two groups receiving bupivacaine postoperatively ($F= 60.0$, $P<0.001$) compared to the saline/saline treatment and the lidocaine/saline treatment ($F= 2.8$). Pain intensity was also lower at 48 hr (Fig. 3, lower panel) in the two groups receiving bupivacaine postoperatively ($F=6.8$, $P<0.05$), while no effect was demonstrated for preoperative lidocaine ($F=0.3$) when analyzed by two-way analysis of variance. The affective component of pain was also significantly reduced by bupivacaine ($F=8.7$, $P<0.01$), but not lidocaine ($F= 1.4$) at 48 hr post-surgery (Table 3). Similar results were seen for the VAS for pain intensity (Table 3).

The time to request for analgesics in the immediate postoperative period varied relative to the duration of the local anesthetic (Table 4). Most subjects in the placebo and lidocaine groups requested postoperative analgesic in the immediate postoperative period (87.0% and 90.9% respectively) in comparison to the bupivacaine or lidocaine plus bupivacaine groups (41.2% and 74.1%). No significant difference was noted in the consumption of acetaminophen (325 mg tablets) over the first 24 hr following surgery or from 24 to 48 hr following surgery. There was a non-significant trend for subjects in the placebo and lidocaine preoperative groups to self-administer more codeine tablets for unrelieved pain (Table 4).

Discussion

The experimental design of the present study permitted differentiation between the effects of intraoperative nociceptive input and postoperative inflammatory pain on the development of

sensitization. The blockade of the intraoperative afferent barrage by preoperative lidocaine did not result in a detectable effect on pain at 24 and 48 hr, suggesting that the intensity and duration of nociceptive input during oral surgery is insufficient to produce central sensitization manifesting as increased pain at later time points. . There was no significant difference between groups in the consumption of analgesics on Days 1 and 2, indicating that differences in pain report at 24 and 48 hr were not confounded by analgesic intake that might attenuate pain or the inflammatory process. In contrast to previous reports (11-13), preoperative blockade of intraoperative nociceptive input alone did not have an effect on pain at 48 hr in this model, suggesting that the relatively brief duration of nociceptive input during oral surgery is a less important stimulus than the more prolonged postoperative pain attributed to inflammation in this model. Other studies using a long duration anesthetic have failed to take into account the carryover of preoperative interventions into the postoperative period, thereby also blocking postoperative pain input contributing to the development of sensitization (13, 34).

The increase in intraoperative plasma concentrations of ß-endorphin in the two groups receiving placebo local anesthetic injections prior to surgery suggests activation of an intraoperative nociceptive barrage sufficient to result in descending hypothalamic-pituitary secretion. The observed increase in plasma ß-endorphin concentration is similar to changes seen in awake subjects undergoing surgical stress or subjected to moderate to severe postoperative pain (21, 22). Local anesthetic blockade of postoperative inflammatory pain input significantly attenuated the nociceptive barrage and β-endorphin release. The findings suggest that the maintenance of central sensitization leading to persistent pain and hyperalgesia is dependent on input from damaged peripheral tissue (23), characteristic of the postoperative period. In

addition, this maintained input occurring postoperatively may be a major contributor to sensitization leading to increased pain at later time points in the oral surgery model.

The postoperative analgesic effects of presurgical interventions are presumed to depend on their ability to attenuate central sensitizaton associated with tissue injury (24). Clinical studies comparing preemptive treatments versus no treatment are overwhelmingly supportive of a beneficial effect in the pretreated patients (11, 13, 25-28) across a wide variety of clinical models and types of surgery. However, studies comparing preemptive versus postsurgical treatment with regional anesthesia have produced conflicting results suggesting limited (29) or no advantage (30) of presurgical over postsurgical treatment. A possible explanation for these discrepant findings is that the development of sensitization may depend more heavily on the peripheral neural barrage that develops during the postoperative period than that due to surgical trauma (24, 31). The relative roles of surgical trauma and postoperative inflammation on the establishment of central sensitization and hyperalgesia may depend on the site of origin of the surgery and its duration. For example, limb and breast surgery, but not abdominal surgery, are responsive to presurgical epidural morphine (32).The present study utilized a short duration surgical model which produced a short neural barrage intraoperatively, but prolonged postoperative pain due to the progression of inflammation sufficient to initiate and maintain central sensitization . In addition to duration of pain, the character and intensity of the pain probably also influences the effectiveness of the preemptiveapproach, as neuropathic pain is not influenced by regional anesthetic block prior to neuronal injury (33, 34). Similarly, demonstration of a preemptive effect of intrathecal lidocaine in rats administered hind paw injections of 2.5% formalin was overcome by administration of 3.75 and 5.0% formalin (24),

indicating that attenuation of the development of central sensitization is dependent on the magnitude of the nociceptive input.

The importance of post-surgical blockade on the prevention of sensitization leading to increased pain at later time points is illustrated by the blockade of both primary and secondary hyperalgesia from carrageenan in rats administered a prolonged (12-16 hr) nerve block with tonicaine (35). Administration of the same anesthetic 5 hr after carrageenan also prevented the development of late hyperalgesia ($\geq$ 24 hr). However, short-term nerve block with lidocaine produced no significant changes in carrageenan –induced hyperalgesia. These observations suggest that nerve blockade should last until noxious input from the inflamed tissues decreases below the level that can maintain central sensitization (24, 31, 35).

Our study suggests that the management of postoperative pain following surgery can be optimized by not only administering long-acting local anesthetics to block pain during the postoperative period, but also by combining the local anesthetic with analgesics to attenuate the development of inflammation over the first few days following surgery. Previous studies in the oral surgery model have demonstrated that suppression of pain over the first 4-8 hr postoperatively by a long-acting local anesthetic (36) is additive with the effects of NSAIDs (37). While not directly tested in these studies, the decrease in pain and inflammation over the same time course as in the present study suggests that administration of NSAIDs to suppress postoperative pain also decreases pain at later time points by suppressing the neural barrage leading to central sensitization.

The continuing controversy over the efficacy of preemptive analgesia (15, 38, 39) is based on semantic concerns over the use of the term “preemptive,” but reflects increasing recognition that the intervention should be applied prior to the nociceptive barrage (whether intraoperative or

postoperative) and provide effective suppression of nociceptive input from the damaged tissues over the time course that normally contributes to the development of sensitization (31). It does not appear to be important whether the intervention is applied preincisional or postincisional to be considered preemptive, but rather that postoperative hyperalgesia is attenuated at later time points by limiting the development of central sensitization. The present study suggests that postoperative pain contributes to a greater extent than intraoperative nociceptive barrage, at least in the oral surgery model. Given the inflammatory nature of postoperative pain, administration of anti-inflammatory drugs in combination with a long-acting local anesthetic should be additive (37, 40) and result in clinically meaningful preemptive analgesia.

Acknowledgement

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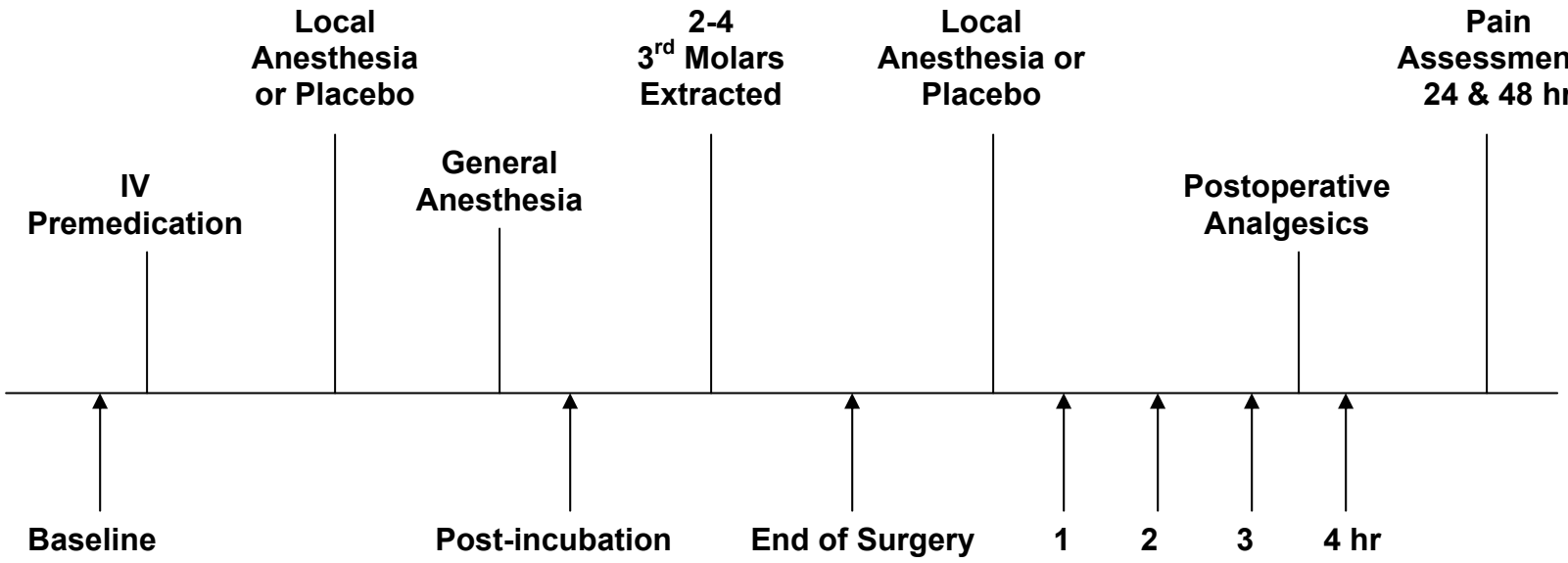
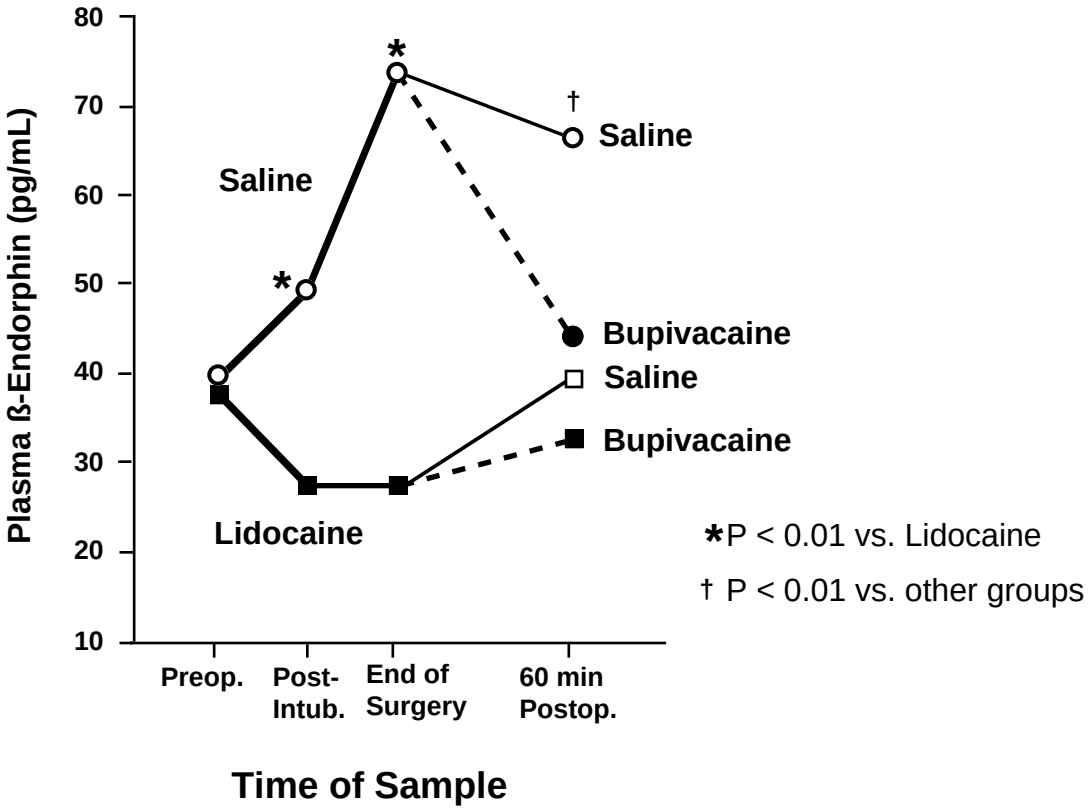
Figure Legends

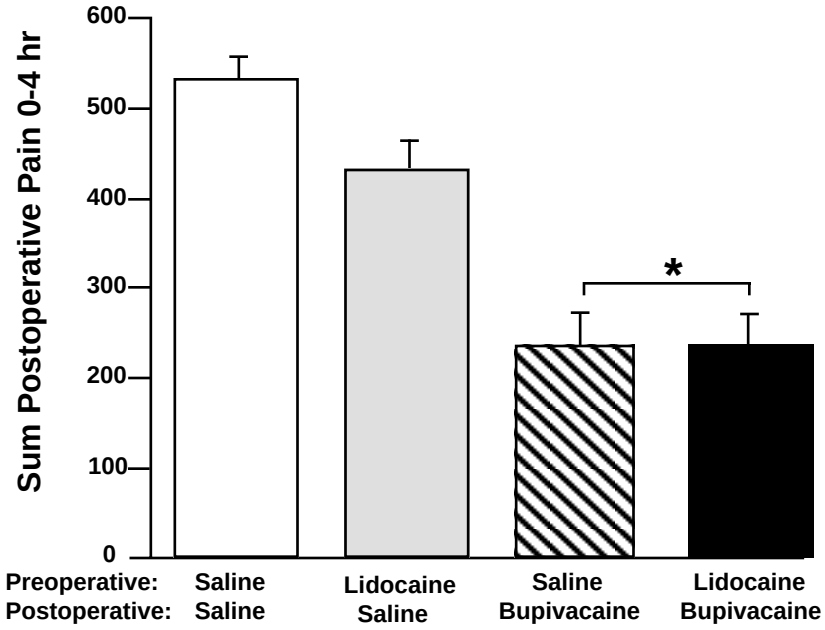
Figure 1. Integration of clinical procedures and data collection. Arrows indicate blood samples collected.

Figure 2. Plasma concentration of immunoreactive ß-endorphin (pg/mL) over time.

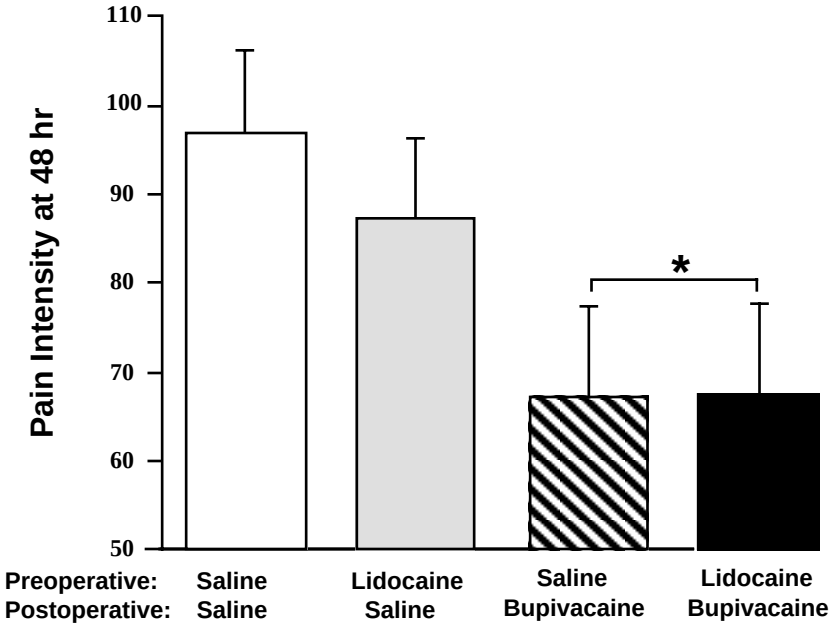
Figure 3. Pain intensity in the immediate postoperative period over the first four hr postoperatively depicted as sum of pain intensity (upper panel) and at 48 hr postoperatively (lower panel) as measured by a 200 mm verbal descriptor scale.


Local Anesthesia or Placebo
2-4 3rd Molars Extracted
Local Anesthesia or Placebo
Pain Assessments 24 & 48 hr
IV Premedication
General Anesthesia
Postoperative Analgesics
Baseline
Post-incubation
End of Surgery
1
2
3
4 hr
Blood Samples


80
70
60
50
40
30
20
10
Plasma ß-Endorphin (pg/mL)
*
†
Saline
Saline
*
Bupivacaine
Saline
Bupivacaine
Lidocaine
Preop.
Post-Intub.
End of Surgery
60 min Postop.
Time of Sample
*P < 0.01 vs. Lidocaine
† P < 0.01 vs. other groups



* P < 0.001 Bupivacaine drug effect, 2-ANOVA



* P < 0.05 Bupivacaine drug effect, 2-ANOVA

Tables

Table 1. Demographic and surgical variables

	Sample Size (N)	Age (yr)	Weight (kg)	Height (cm)	Surgical Difficulty*	Duration (min)
Placebo	23	22.1 ± 3.9	62.3 ± 17.0	168.5 ± 8.4	9.2 ± 0.6	9.1 ± 4.1
Lidocaine Preoperative	22	23.2 ± 5.7	68.8 ± 12.6	169.4 ± 8.6	9.8 ± 0.6	10.2 ± 4.1
Bupivacaine Postoperative	17	21.5 ± 4.6	75.6 ± 34.8	153.3 ± 37.2	9.5 ± 0.6	10.2 ± 6.0
Lidocaine + Bupivacaine	28	22.4 ± 5.1	68.5 ± 25.8	162.5 ± 24.5	8.8 ± 0.7	10.4 ± 5.9

*Sum of surgical difficulty scores for all teeth extracted, where 1= *simple*, 2 = *soft tissue*, 3 = *partial bony*, 4 = *full bony impaction*.
Values are mean ± *SD*

Table 2. Drugs and doses of drugs used for preoperative sedation, general anesthetic and local anesthetic.

					*Local Anesthetic	
	Midazolam (mg)	Propofol (mg)	Succinylcholine (mg)	Atracurium (mg)	Preoperative (mg)	Postoperative (mg)
Placebo	2.9 ± 1.2	449.3 ± 150.3	91.3 ± 39.5	22.3 ± 9.3	0	0
Lidocaine Preoperative	3.1 ± 1.3	440.4 ± 113.5	104.6 ± 32.6	26.8 ± 10.3	236 ± 28.0	0
Bupivacaine Postoperative	2.5 ± 0.6	447.5 ± 160.8	97.6 ± 15.6	19.6 ± 6.1	0	48.5 ± 10.5
Lidocaine + Bupivacaine	3.2 ± 1.6	402.5 ± 162.2	98.6 ± 41.3	25.0 ± 13.8	210 ± 48.0	49.5 ± 13.0

Values are mean ± *SD*

* Similar volumes of local anesthetic solution or matching saline placebo were injected to all subjects (mean volume = 9.7 – 11.8 mL)

Table 3. Pain over initial 4 hours postoperatively and at 24 and 48 hr.

	1 hr	2hr	3 hr	4 hr	Sum 1-4 hr	24 hr	48 hr
Verbal Descriptor Scale for Unpleasantness							
Placebo	111.6 ± 27.6	108.5 ± 26.7	106.5 ± 30.3	107.5 ± 28.2	427.6 ± 104.5	83.4 ± 29.9	84.8 ± 35.7
Lidocaine Preoperative	62.8 ± 43.4	82.1 ± 40.3	109.0 ± 41.3	113.3 ± 40.0	351.6 ± 138.6	77.0 ± 31.3	75.6 ± 34.6
Bupivacaine Postoperative	49.5 ± 30.6	46.4 ± 33.7	53.0 ± 34.4	60.8 ± 26.5	*209.7 ± 116.2	*63.1 ± 34.1	*61.6 ± 36.7
Lidocaine + Bupivacaine	38.6 ± 26.2	45.5 ± 36.1	73.1 ± 38.8	75.4 ± 35.8	*232.6 ± 117.9	*57.9 ± 28.5	*54.2 ± 27.6
Visual Analog Scale							
Placebo	66.5 ± 16.4	66.6 ± 15.9	65.1 ± 17.7	64.8 ± 18.3	263.0 ± 66.1	41.7 ± 24.0	40.1 ± 23.2
Lidocaine Preoperative	30.1 ± 27.1	41.1 ± 26.7	58.4 ± 25.4	60.9 ± 25.5	190.5 ± 89.9	36.6 ± 17.8	36.6 ± 19.7
Bupivacaine Postoperative	16.2 ± 21.0	20.1 ± 22.9	26.2 ± 22.4	31.9 ± 24.4	*94.4 ± 83.8	27.8 ± 25.5	*28.2 ± 24.0
Lidocaine + Bupivacaine	12.0 ± 18.9	17.1 ± 21.0	35.9 ± 25.2	40.5 ± 26.0	*105.5 ± 77.4	32.3 ± 23.6	*27.0 ± 18.7

Values are mean ± *SD*

* Bupivacaine drug effect (2-ANOVA) $P < 0.05$

Table 4. Postoperative analgesic usage over first two days postoperatively.

	0-4 hr		0-24 hr		24-48 hr	
	Time to Medication	Time to Medication (min)	Acetaminophen 325 mg (# tablets)	Codeine 30 mg (# tablets)	Acetaminophen 325 mg (# tablets)	Codeine 30 mg (# tablets)
Placebo	55.9 ± 35.7	87.0	11.3 ± 2.2	1.3 ± 2.6	10.4 ± 3.2	1.6 ± 2.1
Lidocaine Preoperative	122.1 ± 51.0	90.9	10.0 ± 1.6	1.4 ± 1.6	10.2 ± 2.6	1.8 ± 1.8
Bupivacaine Postoperative	227.5 ± 144.1	41.2	9.5 ± 1.6	0.8 ± 1.1	8.1 ± 3.6	0.6 ± 1.1
Lidocaine + Bupivacaine	199.6 ± 89.1	74.1	10.1 ± 2.1	1.8 ± 2.6	10.8 ± 2.5	0.9 ± 1.3

Values are mean ± *SD*